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Cocaine Plasma Concentration: Relation to Physiological and Subjective Effects in Humans

Abstract. *Volunteer subjects with previous histories of cocaine use were administered cocaine hydrochloride intravenously or intranasally. There was a positive relationship between peak plasma concentration, physiological and subjective responses, and dose administered. The rate of cocaine disappearance after intravenous administration paralleled the drop in physiological and subjective drug effects. After intranasal administration, blood levels remained elevated for a considerably longer period.*

The presence of a positive correlation between plasma levels of cocaine in humans and its physiological and subjective effects has been questioned in two recent reports (*1*, *2*). Van Dyck *et al.* (*1*) applied a 10 percent solution of cocaine hydrochloride to the nasal mucosa of surgical patients (who were also given other drugs), and found that the peak concentrations in plasma occurred after approximately 60 minutes. They noted that since maximum euphoria reported by street users occurs within 3 to 5 minutes after inhalation of the drug, the peak plasma levels of cocaine are not related to peak euphoric effects. Resnick *et al.* (*2*) administered cocaine solutions intravenously and intranasally and found that peak drug effects occurred within 5 to 10 minutes after intravenous injection and 15 to 20 minutes after intranasal administration, but did not measure plasma levels. Using for comparison the data of Van Dyck *et al.* (*1*), who measured plasma levels but not subjective effects, Resnick *et al.* concluded that the time course of the physiological and subjective effects is apparently not related to levels of cocaine in plasma.

The present study was designed to correlate physiological and subjective effects with the plasma concentration of cocaine in the same subjects (*3*). Ten adult volunteers with histories of intravenous cocaine use were the subjects. Prior to inclusion in the study, each was given an extensive drug history interview and a thorough psychiatric and physical examination (*4*). Subjects were admitted to the clinical research unit of Billings Hospital for a 2-week period during which they were tested daily with either intravenous cocaine or saline or intranasal cocaine. Cocaine hydrochloride (16 or 32 mg) dissolved in physiological saline was administered intravenously (1 ml in 60 sec) through a previously inserted scalp-vein infusion set. Intranasal cocaine was administered as 100 mg of white powder consisting of the appropriate dose of cocaine (16, 64, and 96 mg) mixed with lactose powder. Subjects were instructed to inhale this mixture through a 5.0-cm straw within 1 minute.

One or two scalp-vein butterfly infusion sets attached to saline drip bags were inserted into arm veins and appropriate physiological monitoring devices were placed on each subject 1.5 hours before drug administration. Heart rate was continuously recorded, and subjects were required to report on their drug "high" and fill out drug effects questionnaires, which included identifying the drug they were given and rating it on a 0 to 10 scale (0 = placebo, 5 = average dose of "street" cocaine, 10 = largest dose of "street" cocaine ever taken) (*5*).

Blood samples were collected through a scalp-vein infusion set. When the route of drug administration was intravenous, blood was withdrawn from the arm opposite to the infusion arm. Sodium fluoride (2.5 mg per milliliter of blood) was added to each sample, which was then mixed and separated into plasma and red blood cells. Cocaine from the sample was extracted without delay and determined by gas chromatographic method using an electron capture detector (*6*). Samples were identified by code only, and the code was not broken until all subjective and physiological data had been analyzed.

Table 1. Plasma concentrations of cocaine after intravenous administration. Cocaine values are given as mean ± standard error; *n*, number of determinations.

Time since drug (min)	Dose			
	16 mg		32 mg	
	Cocaine (ng/ml)	*n*	Cocaine (ng/ml)	*n*
5	221 ± 41	12	308 ± 32	15
10	164 ± 24	14	253 ± 25	19
20	150 ± 22	9	253 ± 45	8
30	109 ± 13	14	170 ± 19	19
60	62 ± 9	14	111 ± 14	20
90	30 ± 3	5	61 ± 10	14
120	21 ± 4	5	49 ± 10	10

Plasma concentrations of cocaine after intravenous injections of 16 and 32 mg are given in Table 1. Plasma levels were higher after the larger dose. There were large intersubject variations in the plasma concentrations in the ten subjects studied (for instance, cocaine plasma concentrations ranged from 86 to 309 ng/ml 5 minutes after a 16-mg injection and from 216 to 409 ng/ml 5 minutes after a 32-mg injection). Half-life of cocaine disappearance from plasma varied from 16 to 87 minutes (*7*). This is the first study of plasma half-life of cocaine in humans after intravenous injection, although Misra (*8*) reported plasma half-life of cocaine after intravenous injection in rats, dogs, and monkeys of 18, 72, and 72 to 78 minutes, respectively.

The rate of cocaine disappearance in human plasma after intravenous injection paralleled the return of heart rate to predrug levels after the peak increase 8 to 12 minutes after cocaine administration (Fig. 1). Although some intersubject variability was seen, changes in heart rate after intravenous cocaine were similar to those previously reported (*4*), with heart rate returning to predrug levels by 30 to 45 minutes. After intravenous injection of drug, subjects reported that the maximum "high" occurred approximately 3 to 5 minutes after injection. They indicated that the drug effect had disappeared within 30 to 40 minutes and that, if self-injecting, they would be ready for a second dose at this time. Both plasma concentration of cocaine and physiological and subjective effects were dose-related. It appears that the cardiovascular and subjective effects are highly correlated with the rapid increase in cocaine plasma levels, peaking early and showing parallel decreases over the first 30 minutes after intravenous injection.

Plasma concentrations of cocaine after different intranasal doses are given in Table 2. Concentrations increased rapidly for the first 20 to 30 minutes after inhalation, reaching peak levels before 60 minutes, and then decreased gradually over the next hour. Higher doses yielded higher peak plasma values. As was ob-

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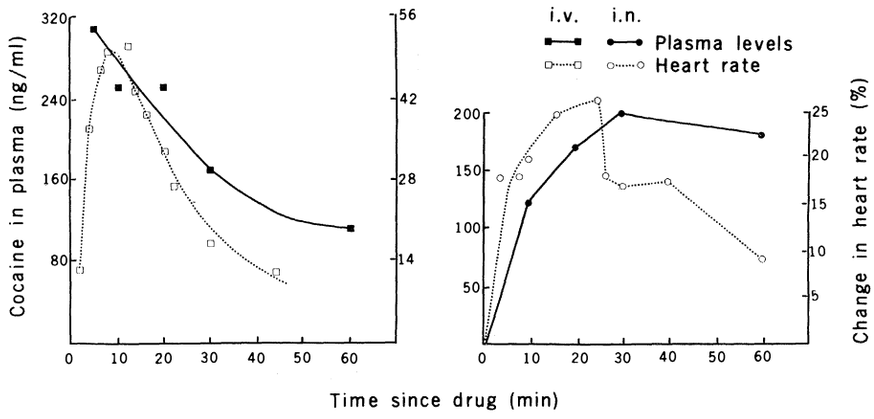

Fig. 1. The relationship between cocaine plasma levels and change in heart rate after cocaine administration (32 mg intravenously or 96 mg intranasally). Heart rate is given as percentage of change from control (30 minutes before drug).

Table 2. Plasma concentrations of cocaine after intranasal administration. Means ± standard error of mean are given; *n*, number of determinations.

Time since drug (min)	Dose					
	16 mg		64 mg		96 mg	
	Cocaine (ng/ml)	*n*	Cocaine (ng/ml)	*n*	Cocaine (ng/ml)	*n*
10	19 ± 4	4	80 ± 19	14	128 ± 32	10
20	17 ± 4	3	112 ± 28	12	173 ± 37	11
30	46 ± 12	4	115 ± 22	13	206 ± 34	12
60	53 ± 12	4	114 ± 21	14	180 ± 30	13
90	31 ± 6	2	51 ± 15	6	126 ± 30	6
120	16 ± 5	2	27 ± 13	6	117 ± 31	5

served after intravenous injection, there were large individual differences in peak plasma concentration after intranasal administration (for example, after 96 mg cocaine peak values ranged between 104 and 533 ng/ml). Similar intersubject variations have been reported after intranasal application to surgical patients (*1*).

The onset of cardiovascular changes paralleled the increase in plasma cocaine levels, with peak values at approximately the same time. In addition, subjects reported that their maximum "high" was 15 to 20 minutes after inhalation. The return to predrug physiological and subjective levels occurred within 60 to 90 minutes, more rapidly than the decrease in cocaine plasma levels.

In general, there was good relationship between the changes in subjective and cardiovascular effects and plasma concentrations of cocaine following intravenous and intranasal administration. After intravenous injection the cardiovascular and subjective effects occurred almost immediately, when the plasma concentration was also maximum. Both dissipated in a roughly parallel manner.

The suggestions (*1*, *2*) that physiological and subjective changes after cocaine administration are not related to plasma levels of cocaine are not supported by this experiment, in which all data were collected in the same subjects. The time course of cardiovascular and subjective effects in the present study is similar to that reported by Resnick *et al.* (*2*) for both intravenous and intranasal administration. Consequently, the time course of plasma levels correlates well with those for subjective and cardiovascular effects reported here and with those observed by Resnick *et al.* (*2*).

The time of maximum plasma cocaine concentration after intranasal administration observed by us differs from that reported by Van Dyck *et al.* (*1*). This difference may be due to the fact that their subjects were undergoing cardiovascular or dental surgery and were given other medications besides cocaine. The most critical factor, however, is that they applied cocaine solution on cotton swabs whereas in our study and that of Resnick *et al.* (*2*) the subjects were given cocaine powder to "snort" as is done in the streets. Since cocaine is a potent vasoconstrictor, slight differences in mode of intranasal administration might markedly alter the rate of absorption.

Although there was a positive relationship between the timing of peak plasma concentrations of cocaine and that of its subjective and cardiovascular effects, plasma levels of drug remained fairly elevated after 60 minutes when subjective and cardiovascular effects had approached base line. This difference was more pronounced after intranasal administration of cocaine. Also, after intravenous administration the cardiovascular effect disappeared slightly faster than cocaine disappeared from plasma. These data suggest that in subjects showing an initial response to cocaine administration, compensatory mechanisms are triggered which result in a faster decline of both cardiovascular and subjective effects than of plasma cocaine concentration.

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